13 Plant Medicines Used in the Treatment of Malaria

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13.1 Introduction

Globally, malaria ranks among the top three communicable killer diseases. Each year, malaria causes 781 000 deaths and illnesses in an estimated 225 million people worldwide (WHO, 2010). Most deaths occur in sub-Saharan Africa (WHO, 2008), with young children and pregnant women at greatest risk for severe forms of malaria and death (WHO, 2008). Uganda has one of the highest burdens of malaria globally, with an estimated 70 000–110 000 children dying of malaria each year (Lynch *et al*., 2005).

At the household and at the national level, malaria exerts significant social and economic costs (Sachs and Malaney, 2002). These costs include direct medical costs to treat the disease and also lost income resulting from inability to work or time taken off work to care for relatives with malaria. Malaria in children impacts negatively on school attendance and decreases savings at the household level. At the national level, governments incur the costs of prevention and treatment of malaria. Furthermore, the economic impact of malaria endemicity includes lower trade, tourism and foreign direct investment (Sachs and Malaney, 2002).

Allopathic medicines are widely used to treat malaria, but traditional medicines are also used (Tabuti, 2008). Historically, allopathic medicines lose effectiveness periodically due to emergence of drug-resistant strains of *Plasmodium* spp., the causative pathogen of malaria. Consequently, widely accessible and affordable medicines, including chloroquine and sulfadoxine–pyrimethamine, are no longer used in the Uganda malaria treatment programme (MOH, 2005). These agents have been replaced by highly efficacious combination therapies containing artemisinin derivatives. For uncomplicated malaria, the World Health Organization recommends artemisinin combination therapy (ACT) containing a rapidly acting and highly potent artemisinin derivative combined with a longer acting less potent partner drug that prevents malaria relapse and may contribute to preventing the emergence of resistance to the artemisinins. Despite this strategy, resistance to artemisinin has begun to appear (Phyo *et al*., 2012).

Consequently, there is an urgent need to identify and develop new therapies that will control malaria. Research for new drugs for the treatment of malaria is highly justified, especially in Africa, because access to efficacious allopathic medicines like ACTs is limited, and were it not because of their being highly subsidized by the donor community or the government, in this case the Ugandan Government, many Ugandans would not have any access at all to ACTs because they are costly.

One of the most effective ways of identifying efficacious and safe medicines is to document indigenous knowledge (IK) associated with traditional medicine in ethnobotanical studies (Balick, 1990; Prance, 1991). Indeed, some of the most effective antimalarials have been developed from traditional medicines, including quinine from the bark of *Cinchona* spp. and artemisinin from *Artemisia annua* L. (annual wormwood). In this chapter we review the plant materials that have been documented so far for the treatment of malaria in Uganda and what evidence exists with regard to the efficacy and safety of these medicinal plants.

13.2 Approach used in the review

We conducted a literature search for published articles on research conducted in Uganda. We included articles in which materials for treatment of malaria were documented. We included articles that were specifically focused on malaria, as well as general ethnobotanical surveys in which malaria treatments were documented alongside other material for treating other diseases. We prioritized the reported medicines using two criteria. First, species mentioned from three and/or more regions in Uganda; second, species which were highly ranked by the author(s). The information on rankings was not uniform, and some authors did not rank the species. We found three reports that reported directly on malaria and seven general ethnobotanical papers that were not explicitly focused on malaria but reported it among other traditional medicines. Most studies aimed at drug discovery for malaria focused on documenting known materials, and only a handful of pharmacological studies have been conducted to evaluate the efficacy and safety of plant species used to treat malaria. Only one validation study was identified, and this focused on the efficacy of *Cardiospermum halicacabum* and *Momordica foetida* (Waako *et al*., 2005). After developing a select species list, we expanded our review to include international articles that reported on the safety and efficacy of plants that had been documented in the Ugandan studies.

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13.3 Plant species commonly used to treat malaria in Uganda

In our review, we identified 129 species used for malaria treatment. Some plant species are used for malaria treatment in more than one region in Uganda (Table 13.1). The finding that these species are known in different ethnic and geographical groups may indicate that these species are efficacious. Using this criterion, we identified 12 species from the 129 species as priority plants for further study (Table 13.1). The remedies are prepared by boiling hard plant parts, like the bark or the root, to prepare decoctions or by crushing leaves and mixing in water (infusions). We found most therapies are prepared from single species; however, some concoctions are prepared from mixtures of species; for example, *Vernonia amygdalina* plus *Momordica foetida*; *Cannabis* sp. plus *Chenopodium opulifolium*; or *Mangifera indica* plus *Tamarindus indica* (Tabuti, 2008).

Studies reported that therapies are administered orally in variable doses; for example, 100–500 mL for adults and older children, or 1–3 tablespoons for children younger than 5 years one to three times a day either for short duration (1–3 days) or until the patient's condition has improved (Tabuti, 2008; Stangeland *et al*., 2011).

For five of the species in Table 13.1 we found articles describing efficacy and safety. This information is summarized below and suggests that some of these species may be active against malaria.

V. amygdalina is used to treat fevers and malaria in several African countries, including Cameroon (Betti, 2004), Nigeria (Tor-anyiin *et al*., 2003), Rwanda (Hutchings *et al*., 1996) and Ethiopia (Karunamoorthi and Tsehaye, 2012). Widespread use of this plant for malaria treatment is further evidence of efficacy and/or safety. In studies reporting the activity of leaf extracts of this plant against *Plasmodium falciparum*, the half maximal inhibitory concentration (IC_{50}), which represents the concentration of the extract at which 50% of parasite is inhibited, ranged from 2.5 to 9.7 μg/mL, depending on solvent used in the extraction (Tona *et al*., 2004; Chenniappan and Kadarkarai, 2010). A review by Magadula and Erasto (2009) indicates that *V. amygdalina* has active sesquiterpenoids, and that the sesquiterpene lactones (STLs) vernodalin, vernodalol, vernolide and hydroxyvernolide have moderate antiplasmodial activity against the multidrug-resistant K-1 strain of *P. falciparum*, with vernodalin being the most active compound with an IC_{50} of 4 μg/mL. Young leaves of *V. amygdalina* contain higher concentrations of vernodalin than the other STLs. This suggests that the observed antimalarial efficacy found especially in leaf extracts of the species may be partly due to vernodalin. In addition, leaves of *V. amygdalina* contain steroidal saponins of the class vernonioside A1, A2, A3, A4 and B1. These saponins were seen to have weak antiplasmodial activity against the multidrug-resistant K-1 strain (Ohigashi *et al*., 1994; Magadula and Erasto, 2009).

Azadirachta indica is used in Tanzania (Gessler *et al*., 1995), Ghana (Abbiw, 1996; Asase *et al*., 2005) Kenya (Njoroge and Bussmann, 2006; Nguta *et al*., 2010), and Nigeria (Sofowora, 1993; Tor-anyiin *et al*., 2003). Antiplasmodial activity of this plant has been demonstrated clinically and experimentally (Sofowora, 1993).

Table 13.1 Plant species most frequently mentioned in literature from Ugandan studies for the treatment of malaria. The table also shows the number of reports encountered in the study and the geographical regions from which the reviewed studies were conducted

Species	No. of reports	Uganda geographical region[a]	Source
Vernonia amygdalina Delile	8	a, b, c, d	Tabuti *et al.* (2003), Ssegawa and Kasenene (2007), Galabuzi (2008), Tabuti (2008), Oryema *et al.* (2010), Stangeland *et al.* (2011)
Azadirachta indica A. Juss.	4	b, c, d	Tabuti *et al.* (2003), Galabuzi (2008), Tabuti (2008), Stangeland *et al.* (2011)
Pseudarthria hookeri Wight &Arn	5	a, c, d	Ssegawa and Kasenene (2007), Galabuzi (2008), Oryema *et al.* (2010), Stangeland *et al.* (2011)
Mangifera indica L.	3	a, b	Tabuti *et al.* (2003), Tabuti (2008)
Momordica foetida Schumch. Et Thonn	4	b, c	Tabuti *et al.* (2003), Tabuti (2008), Oryema *et al.* (2010), Stangeland *et al.* (2011)
Cajanus cajan (L.) Millsp.	3	a, b, c	Tabuti (2008), Stangeland *et al.* (2011)
Zanthoxylum chalybeum Engl.	3	a, b, d	Ssegawa and Kasenene (2007), Galabuzi (2008), Tabuti (2008), Oryema *et al.* (2010)
Markhamia lutea (Benth.) K. Schum.	3	c, d	Galabuzi (2008), Stangeland *et al.* (2011)
Maesa lanceolata Forssk	3	c, d	Galabuzi (2008), Stangeland *et al.* (2011)
Microglossa pyrifolia Kuntze (TS)	3	c, d	Galabuzi (2008), Stangeland *et al.* (2011)
Senna didymobotrya (Fresen.) H.S. Irwin & Barneby	3	c, d	Ssegawa and Kasenene (2007), Stangeland *et al.* (2011)
Vernonia lasiopus O. Hoffm.	3	c, d	Ssegawa and Kasenene (2007), Galabuzi (2008), Stangeland *et al.* (2011)

[a](a) Northern Uganda, includes the Oyam and Erute counties; (b) eastern Uganda, includes studies from Kaliro and Budiope districts close to Lake Kioga; (c) western Uganda, includes Kiohima, Mbarara and Nyakayojo; (d) south western Uganda has Sango Bay region. In the eastern region the study was conducted among people of the Basoga ethnic group, in south western region among the Banyankole and in the northern region among the Acholi.

The active principles are reported to be nimbolide and gedunin (Sofowora, 1993).

Mangifera indica is widely used for the treatment of malaria (Willcox and Bodeker, 2004). In Africa it is used in Ghana (Asase *et al*., 2005), Nigeria (Tor-anyiin *et al*., 2003), Tanzania (Gessler *et al*., 1995) and Rwanda (Hutchings *et al*., 1996). The bark shows moderate to low antiplasmodial activity (IC_{50} 6.76–11.50 μg/mL) depending on solvent used in the extraction (Chenniappan and Kadarkarai, 2010).

Momordica foetida water and ethyl acetate extracts were found to have weak *in vitro* antiplasmodial activity with IC_{50} values greater than 28.00 μg/mL. *In vivo* studies of water extracts of *M. foetida* given orally in the dose range 200 and 1000 mg/kg twice daily prolonged survival of mice infected with *Plasmodium berghei* from 7.0 ± 1.8 to 17.9 ± 1.8 days (Waako *et al*., 2005).

Zanthoxylum chalybeum is used in different countries, including Tanzania (Gessler *et al*., 1995) and Kenya (Njoroge and Bussmann, 2006; Nguta *et al*., 2010), for the treatment of malaria. According to Gansané *et al.* (201), alkaloids from the stem bark are active against *P. falciparum* W2 strain (IC_{50} of 1.2 μg/mL). However, the alkaloids were toxic with a selectivity index (SI) >20. Gessler *et al* (1995) reported high *in vitro* antiplasmodial activity for *Z. chalybeum* root bark obtained from Tanzania (Gessler *et al*., 1994) with IC_{50} of 0.7 μg/mL and 0.43 μg/mL in the ethyl acetate fraction and water fraction respectively. However, the level of activity depended on the plant part and region from which the material was collected. Root bark extracts were more effective than stem bark, while *Z. chalybeum* root bark obtained from the Kagera region was three times more active than root bark samples obtained from Dar es Salaam.

Cajanus cajan (L.) Millsp. is a promising species for malaria treatment. It has been reported for use as an antimalarial in several countries, including Kenya (Njoroge and Bussmann, 2006), Nigeria (Ajaiyeoba *et al*., 2006) and in South America (see references in Duker-Eshun *et al*. (2004)). Crude extracts of this plant contain compounds that have been shown to have antimalarial activity. Duker-Eshun *et al*. (2004) reported IC_{50} values ranging from 19 to 34 μM for stilbenes, longistylin A and C, and betulinic acid, while cajachalcone, 2′,6′-dihydroxy-4-methoxy chalcone is reported to have an IC_{50} value of 2.0 μg/mL (7.4 μM) (Ajaiyeoba *et al*., 2013). The species appears to be non-toxic (Ajaiyeoba *et al*., 2006).

Use of the same species for the same use is one demonstration of the importance of a species, and in this particular case indirect evidence that the species may be effective against malaria. It is also evident that little research has been done to validate plant materials used to treat malaria. There is a need, therefore, to undertake scientific studies to build up scientific evidence for these species with positive implications for drug development.

13.4 Conclusions and recommendations

In this review we found information on many plants known to treat malaria in Uganda. Some species are used in several parts of Uganda, as well as other parts of the world, and this provides initial evidence that these plants may be efficacious for the treatment of malaria. However, for the foreseeable future, allopathic medicines are likely to remain the mainstay of malaria treatment in Uganda and other developing countries. Artemisinins have IC_{50} values in the nanomolar range, representing much greater potency than what is reported for the Ugandan medicinal plants (Basco and Le Bras, 1993). In a Ugandan clinical trial, very high levels of effectiveness were demonstrated (96% cure rate; Achan *et al*., 2009). With the incorporation of ACTs into national treatment programmes and their free distribution to patients diagnosed with malaria, counter-intuitively a significant barrier may exist, to research into medicinal plants for malaria. Although, the limited validation data available from these plants suggest that they are unlikely to be as potent as artemisinins, the combination approach with ACTs suggests that less potent compounds can play an important role in malaria treatment by preventing the emergence of resistant parasites or by synergistic action with existing drugs.

The history of malaria treatment demonstrates that research on medicinal plants can result in the development of highly efficacious, life-saving medicines. It is therefore surprising that so limited published data on medicinal plants are available for malaria treatment in Uganda, where malaria is endemic. Indeed, where these plants are documented, limited information exists with regard to the efficacy or safety of the extracts and more studies are required to confirm their viability as antimalarial agents. We recommend further study of the 12 species that were prioritized in this review. National databases containing information of identity, safety and efficacy of medicinal plants for malaria will facilitate future research in this field.

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